

## **REMARKS**

Claims 1-19 are pending. Claims 1, 3, and 4 are under examination. Claim 3 has been amended to reword what is meant by the term "APP substrate" so as clarify the claimed method. Claim 1 has been canceled and re-added as new claim 20. Accordingly, this amendment and new claim 20 do not raise an issue of new matter and entry thereof is respectfully requested.

### **Regarding the Information Disclosure Statement**

Applicants will submit the NPL for consideration under separate cover.

### **Regarding the Election/Restriction**

The Examiner incorrectly states that Applicant did not traverse the species election requirement in their submission dated January 28, 2008. The original restriction requirement as well as the subsequent species election requirement were expressly traversed by Applicant in the replies dated February 21, 2007 and January 28, 2008, respectively.

### **Regarding the Claim Objection**

Claim 1 is objected to because it depends from a higher numbered claim. Applicants respectfully submit that this is not a proper objection. It routinely happens that during prosecution claims are amended in a manner that results in one or more claims depending on higher numbered claims. Nevertheless, claim 1 has been cancelled and added as new claim 20 and removal of the objection is respectfully requested.

### **Regarding 35 U.S.C. § 112, Second Paragraph**

Applicants respectfully traverse the rejection of claims 1, 3 and 4 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

While the Office Action provides a basis for rejecting claim 3, in particular that it is allegedly unclear what an APP substrate is, no basis is given for the rejection of claims 1 and 4. Applicant assumes that the reason is that claims 1 (now new claim 20) and 4 depend on claim 3.

Base claim 3 has been amended to recite that the substrate comprises APP to more address the basis for the rejection, which has been rendered moot. Applicants respectfully request removal of the rejection of claims 1 (now new claim 20), 3 and 4 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

**Regarding 35 U.S.C. § 103**

Applicants respectfully traverse the rejection of claims 1 (now new claim 20), 3 and 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nagao et al., Tetrahedron Letters, 41, 2419-2424, (2000), in view Mackay EA et al., Eur J. Biochem. Mar 1; 244(2):414-25, (1997).

Briefly, base claim 3 is directed to a method of selecting an agent that prevents cleavage of a substrate comprising APP, said method comprising the steps of contacting a candidate agent with a  $\beta$ -secretase species selected from the group consisting of cathepsin B and cathepsin L, wherein the contacting occurs in the presence of a substrate comprising APP and under conditions that allow for cleavage of the APP by said  $\beta$ -secretase species; and selecting the agent that prevents the cleavage of the APP by the  $\beta$ -secretase species.

The Examiner contends that it would have been obvious to modify the assay taught by Nagao et al. and substitute the cathepsin B peptide substrate, Z-L-Phe-L-Arg-MCA, with APP, because Mackay et al. teach that APP is a substrate for cathepsin B.

The Examiner's argument is not supported by the references upon which it relies. There is no motivation to combine the two cited prior art references, which clearly show that the substrate used in the assays described by Nagao et al., which is a dipeptide capped at both ends, is distinct from the cleavage sites recognized by cathepsin B in the APP protein. Figure 6, panel C, shows the cleavage sites recognized by cathepsin B and not one of them consists of the amino acids F – Phenylalanine (Phe) and R - Arginine (Arg). Accordingly, the inhibition of enzymatic hydrolysis of a capped dipeptide that bears no resemblance to the cleavage sites recognized in the APP protein, would be considered unrelated and irrelevant by the skilled person, who would lack any motivation to combine their respective teachings.

Applicants respectfully request removal of the rejection of claims 1 (now new claim 20), 3 and 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nagao et al., Tetrahedron Letters, 41, 2419-2424, (2000), in view Mackay EA et al., Eur J. Biochem. Mar 1; 244(2):414-25, (1997).

**CONCLUSION**

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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